Experts' Review and Rating of Proposed Hypotheses

I. Introduction

The Lewin Group requested five individuals, identified for their expertise in child health and development, to review the proposed hypotheses to determine their overall level of importance as research priorities and the feasibility of investigating the hypotheses in a large cohort study such as that currently being planned for the *National Children's Study*. The five experts who participated in this effort included:

Thomas DeWitt, M.D., F.A.A.P.
Director, General and Community Pediatrics
Cincinnati Children's Medical Center

Michael Katz, M.D.
Vice President for Research
March of Dimes

Michael Kramer, M.D.
Professor
Departments of Pediatrics and of Epidemiology and Biostatistics
McGill University

George Rhoads, M.D., M.P.H.
Director
Environmental Health Division
Environmental and Occupational Health Sciences Institute

Ruth Stein, M.D., F.A.A.P.
Professor and Vice Chairman of Pediatrics
Albert Einstein College of Medicine

The Lewin Group requested each expert reviewer to rate and provide detailed feedback on each of the 29 hypotheses. The reviewers received a set of criteria to guide the review process, as well as brief descriptions of previous research findings that supported each hypothesis.[2] After reviewing the experts' written comments, Lewin conducted conference calls with each reviewer to clarify and elaborate on their comments and solicit additional feedback.

II. Overall Rating of Level of Importance of Proposed Hypotheses

Reviewers provided a rating of the perceived level of importance (low, medium, or high) of each hypothesis. The Lewin project team examined the distribution of scores for each hypothesis to assign an overall rating, across the five expert reviewers, for each hypothesis. In addition, we applied a quantitative approach to facilitate interpretation of the qualitative *level of importance* ratings provided by the expert reviewers. Lewin applied numeric point values to

[2] Expert reviewers also received (a) a description of The Lewin Group's methodology and approach to reviewing the scientific literature to arrive at the identified targeted research areas and specific hypotheses, and (b) financial compensation for their participation in the hypothesis review process.

each rating experts provided, whereby Low=1; Low/Medium=2; Medium = 3; Medium/High=4; and High=5. We then tallied the total points assigned to each hypothesis to arrive at a summary rating that reflects the overall level of importance given to each hypothesis. Hypotheses that accumulated a total of:

- 17 – 19 points are categorized as *Medium to High*,
- 14 – 16 points are *Medium*;
- 10 – 13 points are *Low to Medium;* and
- less than 10 points are categorized as *Low* level of importance.

Lewin subjectively classified into the priority categories the five hypotheses (Hypotheses 14, 15, 16, 25 and 27) for which only four of five expert reviewers provided overall ratings. Our subjective categorization was based on examination of the distribution of specific responses given for these hypotheses. For example, one reviewer rated Hypothesis 14 as having a low level of importance; two rated it as being of medium importance, and one rated it as having a medium/high level of importance. Given the distribution of ratings provided, Lewin categorized Hypothesis 14 as being of *medium* importance for inclusion in the NCS.

Though this method provides only a rough estimate of the prioritization of each hypothesis, we intend the summary rating to assist NCHS in determining the relative level of importance of each hypothesis from the expert reviewers' perspectives.

Below we present the individual ratings provided by the five expert reviewers for each hypothesis (indicated by a checkmark) as well as the overall summary rating based on our quantitative scoring system. Following this table we present the 29 hypotheses organized by the *Level of Importance* summary ratings (i.e., *Medium to High; Medium,* etc.) to facilitate identification of those hypotheses expert reviewers rated as lower versus higher priority for NCS research. These tables also provide an annotated description of each hypothesis; refer to the *List of Hypotheses* section of this notebook for a detailed listing of the 29 proposed hypotheses.

Hypothesis #	Hypothesis Focus	Level of Importance					Overall Summary Rating[3] (score)
		Low	Low/Medium	Medium	Medium/High	High	
ASTHMA AND OTHER RESPIRATORY ILLNESSES							
1	Infection		✓	✓✓		✓✓	Med/High (18)
2	Endotoxin exposure	✓✓		✓	✓	✓	Medium (14)
3	Maternal exposure to environmental agents /behavior	✓✓				✓✓✓	Med/High (17)
4	Exposure to environmental agents in home	✓✓		✓		✓✓	Medium (15)
5	Exposure to air pollutants	✓✓			✓✓✓		Medium (14)
CHILDHOOD CANCERS							
6	Exposure to EMFs	✓✓✓✓	✓				Low (6)
7	Exposure to solvents and paints	✓✓✓	✓			✓	Low/Med (10)
8	Exposure to insecticides/pesticides	✓✓✓✓			✓		Low (8)
9	Paternal/maternal smoking	✓✓	✓	✓✓			Low/Med (10)
10	Exposure to infectious agents/viruses	✓✓✓✓			✓		Low (8)
ENDOCRINE DISRUPTERS							
11	Reproductive/physiological abnormalities	✓✓✓		✓		✓	Low/Med (11)
ENVIRONMENTAL TOXICANTS							
12	Contaminants in water	✓✓		✓		✓✓	Medium (15)
13	Environmental toxicants and child development	✓✓		✓✓		✓	Low/Med (13)
14	Environmental toxicants (e.g., pesticides) and childhood diseases	✓		✓✓	✓		Medium (11)
INJURY							
15	Immediate environment (home)	✓		✓		✓✓	Medium (14)
16	Physical/psychological stress	✓✓✓				✓	Low (8)
17	Built environment	✓✓✓		✓	✓		Low/Med (10)
18	Psychosocial factors outside home	✓✓		✓✓✓			Low/Med (11)
NEURODEVELOPMENT & BIOBEHAVIORAL DEVELOPMENT							
19	Organophosphates	✓		✓✓		✓✓	Med/High (17)
20	Autism and vaccines/immunizations	✓✓		✓	✓	✓	Medium (14)
21	Stress, neglect and trauma	✓		✓✓✓		✓	Medium (15)
22	Maternal immune response to infections	✓✓✓		✓		✓	Low/Med (11)
23	Methylmercury			✓✓		✓✓✓	Med/High (21)
24	Lead	✓	✓	✓		✓✓	Medium (16)
25	Lead and IQ/cognitive dysfunction	✓✓		✓		✓	Low/Med (10)
26	Maternal factors (smoking, ETS, substance abuse)	✓	✓		✓	✓✓	Med/High (17)
27	Neighborhood and community conditions	✓			✓✓	✓	Med/High (14)
OTHER RESEARCH							
28	Obesity and altered intrauterine environment	✓		✓		✓✓✓	Med/High (19)
29	Infectious bacterial agents and SIDS	✓✓✓	✓	✓			Low (8)

[3] While most hypotheses were rated by all five expert reviewers, Hypotheses 14, 15, 16, 25 and 27 only received four ratings.

Targeted Research Area	Hypothesis Focus	Hypothesis #
MEDIUM TO HIGH		
Asthma	Infection	1
Asthma	Maternal exposure to environmental agents/behavior	3
Neuro- and biobehavioral development	Organophosphates	19
Neuro- and biobehavioral development	Methylmercury	23
Neuro- and biobehavioral development	Maternal factors (smoking, ETS, substance abuse)	26
Neuro- and biobehavioral development	Neighborhood and community conditions	27
Other – Obesity	Obesity and altered intrauterine environment	28
MEDIUM		
Asthma	Endotoxin exposure	2
Asthma	Exposure to environmental agents in home	4
Asthma	Exposure to air pollutants	5
Environmental toxicants	Contaminants in water	12
Environmental toxicants	Environmental toxicants (e.g., pesticides) and childhood diseases (asthma, neurological disorder)	14
Injury	Immediate environment (home)	15
Neuro- and biobehavioral development	Autism and vaccines/immunizations	20
Neuro- and biobehavioral development	Stress, neglect and trauma	21
Neuro- and biobehavioral development	Lead	24
LOW TO MEDIUM		
Childhood cancers	Exposure to solvents and paints	7
Childhood cancers	Paternal/maternal smoking	9
Endocrine disrupters	Reproductive/physiological abnormalities	11
Environmental toxicants	Environmental toxicants and child development	13
Injury	Built environment	17
Injury	Psychosocial factors outside home	18
Neuro- and biobehavioral development	Maternal immune response to infections	22
Neuro- and biobehavioral development	Lead and IQ/cognitive dysfunction	25
LOW		
Childhood cancers	Exposure to EMFs	6
Childhood cancers	Exposure to insecticides/pesticides	8
Childhood cancers	Exposure to infectious agents/viruses	10
Injury	Physical/psychological stress	16
Other – SIDS	Infectious bacterial agents and SIDS	29

III. General Comments and Suggestions Provided by Expert Reviewers

Each of the expert reviewers provided general comments for the proposed hypotheses and for the *National Children's Study*. These comments are listed in the reviewers' own words to preserve the context and tone of the experts' feedback.

1. Overall, Dr. Katz found that many of the hypotheses were too vague or incorporated too many independent and/or dependent variables. He suggests that these hypotheses be teased out and separate hypotheses be derived to examine relationships between specific exposures and specific outcomes of interest; a specific and precise single question is needed for each hypothesis. There is also a potential for numerous confounders for some of the hypotheses proposed. Dr. Katz stressed that controlling for such confounders will be necessary but difficult.

2. Dr. DeWitt noted that randomized control trials will likely be needed in order to answer some of the questions raised in the proposed hypotheses.

3. Dr. DeWitt found that the issue of poverty emerges in many of the proposed hypotheses. Given this fact, the issue of how to measure poverty is important. A good definition of poverty and perceived poverty will be essential.

4. Dr. Rhoads believes that asthma should be an important endpoint for NCS. Though he recognizes that asthma is too common a disorder to warrant or justify the sample size of the NCS study, he feels that NCS would provide an opportunity to examine a variety of environmental factors that might help explain the changing incidence of asthma, especially within different ethnic groups and different rural and urban settings.

5. Dr. Kramer rated the majority of the proposed hypotheses in the area of asthma and other respiratory diseases as low level of importance for the *National Children's Study*. In his opinion, there is little good data to support these hypotheses. He strongly suspects, for example, that overall early infections are increasing, so how would one account for the claims of the hygiene hypothesis? No one has been able to explain why asthma is on the rise, despite increasing infection.

6. The area of childhood cancers is problematic, according to Dr. Kramer, Dr. Rhoads and Dr. Stein, given how rare the outcomes are. The sample size of the *National Children's Study* would be too small to see an effect and may not be the most efficient method for studying childhood cancers. In a sample of one hundred thousand children, one would expect approximately two hundred cases, which would not justify the outcome and the efforts to study these hypotheses. Dr. Kramer suggested that if a component of the *National Children's Study* is to store biomarkers, a nested case control study of childhood cancers may be possible.

7. Additional areas of research for which the sample size of the *National Children's Study* may be insufficient include birth defects and the effects of endocrine disrupters. Outcomes from these areas of research would be too rare to study in a sample size of 100,000 children.

8. Exposure at the prenatal stage appears in many of the hypotheses. Dr. DeWitt suggested that measuring exposure at this stage, however, will be difficult, especially if the prenatal stage is broken down into trimesters. He feels this is almost a dichotomous variable in that we may only be able to study exposed versus not exposed.

9. Two areas of research focus, obesity and neurodevelopment and biobehavioral development, are major epidemics in the United States. Dr. DeWitt noted that both are non-infectious and have multifactoral causes. Even though the outcomes are common, a large study is necessary because of multiple predictors. He suggested that analogous to the Mr. Fit study, investigating the impact of such predictors on adult health could be very significant. A major focus for these research areas should be on childhood antecedents of major adult diseases.

10. Dr. DeWitt was struck by how few of the hypotheses addressed or commented on genetic predisposition/genetic components, given this is the age of the Human Genome Project. He feels that genetic issues have to be more prominent in the *National Children's Study*, and that such issues may influence the design of how some of the proposed hypotheses may be explored.

11. Dr. Kramer indicated that he was surprised at the limited research that surfaced from a review of the literature. He suspects the date parameter used to limit the search to literature from the past five years is one reason the search yielded less research than he expected. He feels there is probably extant literature from before 1996 that would have better informed the proposed hypotheses and areas of research.

IV. Potential Areas for Further Research

Some of the expert reviewers offered suggestions for additional areas of research to consider during the hypothesis generation phase of the *National Children's Study*. These broad areas of research and specific recommendations are provided below.

1. ***The impact of Internet and video game use on behavior.*** Dr. DeWitt suggested one area warranting further research is the effect of the home environment on child health and development. In particular, Dr. DeWitt is theoretically concerned with the impact of children's use of the Internet, video games, etc. There has been little good research on this area of exposure and its potential outcomes, however, it has come up increasingly as an area of exposure for a vast number of children. The Children, Youth, and Families Board of the Institute of Medicine has even examined the issue. Dr. DeWitt's concern is that such an exposure may have effects three to four years from now and may potentially affect behavior outcomes, such as ADHD and stress. His sense is that there is a cusp of opportunity to include this area in the *National Children's Study* as a beginning wave for further research.

2. ***The impact of social and familial influences on obesity.*** Dr. Kramer feels that the research cited in the proposed obesity hypothesis is contrary to traditional thinking. Instead, he feels research in this area should focus on potential social, familial, and societal causes of obesity such as the lack of physical activity at home and at school,

watching television, playing video games, etc. One could look at familial patterns of exercise and parental dietary habits. These are mundane environmental influences but are the most complicated influences to study. Dr. Kramer asserted that obesity, along with asthma, is one of the biggest public health issues we face; so little focus on obesity would be inappropriate. The *National Children's Study* should also consider hypotheses in this research area that could potentially be linked to intervention studies at some point.

3. ***The impact of environmental noise on child health and development.*** Another research area of concern for Dr. Kramer is the potential effect of environmental noise. We have noisier environments than we used to have. Children are listening to loud music and attending concerts. Noise may effect things such as hearing, stress levels, and school performance. Dr. Kramer noted that everyone talks about the potential harm of noise, however little research exists.

4. ***Birth defects*** is an area Dr. Rhoads recommended for inclusion or to be added as a subset to an existing set of hypotheses. Dr. Rhoads noted that the NCS would serve as a great opportunity to study this area, and recommended looking prospectively to examine antecedents of common birth defects such as ventricular septical and neural tube defects, and oral cleft disorders.

V. Ratings and Specific Feedback for Each Hypothesis

The Lewin Group has synthesized the ratings and comments provided by expert reviewers for each of the 29 proposed hypotheses. Reviewers rated each hypothesis in terms of its:

- Public health significance,
- Feasibility and appropriateness for study given the *National Children's Study* design and methodology,
- Relevance given the status of current research and need for future research, and
- Overall level of importance for additional research.

Expert reviewers also provided feedback on many of the hypotheses. The reviewers' specific comments are provided after each hypothesis' summary ratings.[4] We have presented reviewers' comments as they were presented during either our discussions with them or in their written format in order to preserve the context and tone of their individual feedback.

[4] For the purposes of maintaining the anonymity of expert reviewers in this report, The Lewin Group designated a number for each reviewer. Each expert reviewer is identified consistently by his or her designated number throughout this summary section.

HYPOTHESIS #1

Infections in early childhood have a protective effect against asthma.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**2**		**3**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society							**5**
d. Frequency/load of exposure							**5**
e. Special populations in which exposure/disease outcome appears			**1**		**1**		**3**
Overall rating for Public Health Significance						**1**	**4**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**2**		**1**		**2**
b. Ascertaining the exposure and outcome			**1**		**2**		**2**
c. Sample size needed to detect associations			**3**		**1**		**1**
d. Potential for follow-up/tracking					**2**		**3**
e. Generalizability to total population at risk			**1**		**2**		**2**
Overall rating for NCS Study Design Considerations			**1**		**3**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **0** No response
- **0** No basis to judge
- **4** This hypothesis addresses established research
- **1** This hypothesis addresses new and emerging research
- **1** Other (hypothesis not properly studied and probably can't be)

Please rate the need for further research:

- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
0	**1**	**2**		**2**

HYPOTHESIS #1

Infections in early childhood have a protective effect against asthma.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW to MEDIUM

- This research question can be answered in a smaller population study. The major benefit of doing this in the NCS would be if subtypes of infections (like Hypothesis #2) have particular protective effects. There is also a need for controlling other confounders. (Reviewer #1)

MEDIUM

- The assumption that daycare attendance = infections is soft; one cannot assume that merely attending daycare is a surrogate for infections. There are other aspects of this, for example, emotional considerations. It would be very difficult to set up such a study because it would require a very large cohort with many confounders. A consideration of vaccines would need to be included. This hypothesis is of medium importance; early childhood infections are worth studying. (Reviewer #2)

- There is nothing new or original here. Also, why should early infection be decreasing if daycare attendance is increasing? (Reviewer #3)

HIGH

- Early infection would be an important exposure to measure. (Reviewer #4)

- I would rate this hypothesis relatively high, although it is not clear that a study of this magnitude is needed. (Reviewer #5)

HYPOTHESIS #2

Endotoxin exposure in childhood may have a protective effect against the development of asthma.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**2**		**3**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society							**5**
d. Frequency/load of exposure		2	**1**		**1**		**1**
e. Special populations in which exposure/disease outcome appears			**1**		**1**		**3**
Overall rating for Public Health Significance					**1**		**4**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**3**				**2**
b. Ascertaining the exposure and outcome		1	**2**		**1**	**1**	
c. Sample size needed to detect associations			**2**		**1**		**2**
d. Potential for follow-up/tracking			**1**		**2**		**2**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations			**1**		**1**	**1**	**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **0** This hypothesis addresses established research
- **4** This hypothesis addresses new and emerging research
- **1** Other (current research is based on past studies)

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **4** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**1**	**1**	**1**

HYPOTHESIS #2

Endotoxin exposure in childhood may have a protective effect against the development of asthma.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- The hypothesis cannot be tested as stated here. This is a sketchy hypothesis that is based on poor preliminary data and is full of confounders. There is a whole range of endotoxins children are exposed to. One could address this question by looking at the pertussis vaccine [which is a source of endotoxin exposure]. The early pertussis vaccines had different concentrations of endotoxins. One would have to pay attention to this fact. (Reviewer #2)

- The infection and asthma area is a mess. Several studies are post hoc, in that they are trying to fit the evidence to the hypothesis. This hypothesis is not clear enough. What endotoxins would be studied? There are more than just one endotoxin. Lower respiratory tract infections can increase risk for asthma while other infections decrease the risk. This hypothesis would have to be better specified and detailed, and include which endotoxins are of interest and at what age the exposure would be measured. If better stated, the hypothesis could be very useful. (Reviewer #3)

MEDIUM

- It is not clear what proportion of the population is exposed to endotoxins and how this is likely to be manipulated even if found to be protective. The exposure is difficult to measure or determine especially without good cumulative biological measures. Endotoxins don't stay around in the body; it would be tough to catch the precise timing of when subjects have it and to determine when the exposure took place. I am not clear on what would happen with the information if an association was found. What would be the implications? (Reviewer #5)

MEDIUM to HIGH

- This hypothesis begins to look at mechanistic interactions between the environment and asthma. This hypothesis should be adopted. (Reviewer #1)

HIGH

- I am not familiar with the feasibility and reliability of measuring endotoxin exposures. (Reviewer #4)

HYPOTHESIS #3

Maternal exposures to environmental agents (e.g., indoor allergens or environmental tobacco smoke), behaviors (e.g., diet, history of asthma) or complications (e.g., early labor, maternal health complications) during pregnancy may contribute to the development of asthma and other respiratory illnesses in offspring.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**2**		**3**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society							**5**
d. Frequency/load of exposure					**1**		**4**
e. Special populations in which exposure/disease outcome appears		**1**	**1**		**1**		**2**
Overall rating for Public Health Significance	**1**						**4**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**1**		**2**		**2**
b. Ascertaining the exposure and outcome			**2**		**1**	**1**	**1**
c. Sample size needed to detect associations					**1**		**4**
d. Potential for follow-up/tracking			**1**		**1**	**1**	**2**
e. Generalizability to total population at risk			**1**		**1**		**3**
Overall rating for NCS Study Design Considerations			**1**		**1**		**3**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **1** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **1** Other (hypothesis addresses no acceptable research)

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **2** Somewhat needed
- **3** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**0**	**0**	**3**

HYPOTHESIS #3

Maternal exposures to environmental agents (e.g., indoor allergens or environmental tobacco smoke), behaviors (e.g., diet, history of asthma) or complications (e.g., early labor, maternal health complications) during pregnancy may contribute to the development of asthma and other respiratory illnesses in offspring.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This is a "fishing expedition" in a pond devoid of fish! So much nonsense listed that it doesn't merit consideration. One exception: genetic studies may be useful. This hypothesis needs to be split up. The questions need to be isolated, focused, and precise. Any one of these factors has been established as contributing to asthma. None of these factors has been shown to be an antecedent of asthma. Preemies can have respiratory problems which may predispose them to asthma and may be worth studying. Sophisticated genetic studies of polymorphisms may also be of value. (Reviewer #2)

- Diet and environmental exposures are difficult to measure with validity and precision. Also, which exposures to measure is unclear. (Reviewer #3)

HIGH

- Genetic screening coupled with improving techniques for ascertaining exposure make this more feasible. The assessment of multiple exposures (many cells) makes this quite appropriate for the NCS. This hypothesis should be adopted. (Reviewer #1)

- Maternal exposures and obstetric factors appear to be feasible risk factors to examine. (Reviewer #4)

- These are frequent exposures. (Reviewer #5)

HYPOTHESIS #4

Exposures to environmental agents found in the home, such as environmental tobacco smoke (ETS) or indoor allergens, in early childhood may lead to the development or exacerbation of asthma.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**2**		**3**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society							**5**
d. Frequency/load of exposure					**2**		**3**
e. Special populations in which exposure/disease outcome appears		**1**			**2**		**2**
Overall rating for Public Health Significance					**1**		**4**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome					**1**		**4**
b. Ascertaining the exposure and outcome					**2**	**1**	**2**
c. Sample size needed to detect associations					**1**	**1**	**3**
d. Potential for follow-up/tracking			**1**		**1**	**1**	**2**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations					**2**	**1**	**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **1** No response
- **0** No basis to judge
- **3** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**1**	**0**	**2**

HYPOTHESIS #4

Exposures to environmental agents found in the home, such as environmental tobacco smoke (ETS) or indoor allergens, in early childhood may lead to the development or exacerbation of asthma.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis has been shown to be true. However, it address the problem of exacerbation of asthma, not its cause. There is no reason to study this further. There is already enough research available. (Reviewer #2)

- Exposure to environmental tobacco smoke is decreasing, but asthma is increasing. (Reviewer #3)

MEDIUM

- It is not clear that this size study is needed to check this hypothesis. (Reviewer #5)

HIGH

- As in Hypothesis #3, study of multiple exposures requires large sample sizes. This is a significant epidemic in special (poor) populations. (Note: Dr. Lamphear is a colleagues and in my division) (Reviewer #1)

- Environmental exposures in the home appear to be feasible to examine as potential risk factors. (Reviewer #4)

HYPOTHESIS #5

Exposure to air pollutants such as ozone and particulate matter may lead to the development or exacerbation of asthma.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**2**		**3**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society							**5**
d. Frequency/load of exposure					**2**		**3**
e. Special populations in which exposure/disease outcome appears		**2**					**3**
Overall rating for Public Health Significance						**2**	**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**1**		**2**		**2**
b. Ascertaining the exposure and outcome			**2**		**2**		**1**
c. Sample size needed to detect associations							**5**
d. Potential for follow-up/tracking					**3**	**1**	**1**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations			**1**		**2**		**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **2** No response
- **0** No basis to judge
- **2** This hypothesis addresses established research
- **1** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **1** Not needed at all
- **2** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**0**	**0**	**3**

HYPOTHESIS #5

Exposure to air pollutants such as ozone and particulate matter may lead to the development or exacerbation of asthma.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis is of low importance because there's enough information available. (Reviewer #2)

- A difficulty with examining air pollution as a risk factor is that all children at a given clinical center are likely to be exposed to similar amounts and types of air pollution. Thus, a study of this risk factor might turn out to be an ecological study comparing asthma rates at the different centers and relating them to air pollution data. (Reviewer #4)

HIGH

- This is thought to be a major reason for the increase in the incidence of asthma. It is important to link this to genetic predisposition (Eggleston paper). This hypothesis should be adopted. (Reviewer #1)

- Some air pollutants seem to be increasing. They could be a major cause for the increase in asthma. Genetic predisposition may also play a role in the effect of air pollutants on the development and exacerbation of asthma. (Reviewer #3)

- This is likely to be an increasing issue in light of increasing ozone exposure. (Reviewer #5)

HYPOTHESIS #6

Exposure to electromagnetic fields (EMFs) may increase the risk of childhood cancers such as leukemia (acute lymphocytic and T-cell) and brain tumors.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**2**		**2**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual							**5**
➢ for population/society			**2**	**1**	**1**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual							**5**
➢ for population/society			**2**		**2**		**1**
d. Frequency/load of exposure		**1**			**3**		**1**
e. Special populations in which exposure/disease outcome appears		**1**	**1**		**2**		**1**
Overall rating for Public Health Significance			**1**		**3**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**1**		**2**		**2**
b. Ascertaining the exposure and outcome			**1**		**4**		
c. Sample size needed to detect associations			**3**		**1**		**1**
d. Potential for follow-up/tracking			**1**		**1**	**1**	**2**
e. Generalizability to total population at risk			**1**		**2**		**2**
Overall rating for NCS Study Design Considerations			**3**		**1**	**1**	

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **4** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **1** Other (This hypothesis has been studied sufficiently)

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **3** Not needed at all
- **2** Somewhat needed
- **0** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
4	**1**	**0**	**0**	**0**

HYPOTHESIS #6

Exposure to electromagnetic fields (EMFs) may increase the risk of childhood cancers such as leukemia (acute lymphocytic and T-cell) and brain tumors.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis is of low importance because this type of research is best done in animal models until research shows some specific association to warrant the initiation of human epidemiological studies. (Reviewer #2)

- What will the NCS do that is new and original? Cancers are too rare to be studied in a cohort of 100,000. (Reviewer #3)

- One hundred thousand children is not likely to yield enough cases of childhood cancer to justify this outcome. Measuring EMF would take a lot of special effort, and the advantage of the cohort approach over the case-control studies that have already been done is not clear. (Reviewer #4)

- There is insufficient power in the study to detect an effect; the incidence of cancer isn't very high, coupled with the existence of specific subtypes and etiology. There may be only 100 kids with cancer in the study. This hypothesis can be done in a population study that isn't longitudinal. (Reviewer #5)

LOW to MEDIUM

- This is a longstanding controversy, though exposure to EMFs is probably increasing (any data about this?). This may need to be more definitively resolved. There has been research around this for a long time studying power lines. I would omit further study of power lines. There is a burgeoning exposure to EMFs associated with the increased use of computers that is not being addressed in the research. I don't know how strong these fields are. Are we going into an era where kids have more exposure and proximity to computers? (Reviewer #1)

HYPOTHESIS #7

Exposure to solvents and paints may increase the risk of childhood cancers, including leukemia and brain tumors.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**3**		**1**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual							**5**
➢ for population/society			**2**	**1**	**1**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual							**5**
➢ for population/society			**3**		**1**		**1**
d. Frequency/load of exposure		**1**	**1**		**3**		
e. Special populations in which exposure/disease outcome appears	**1**	**1**	**1**		**2**		
Overall rating for Public Health Significance	**1**			**1**	**2**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**1**	**1**	**2**		**1**
b. Ascertaining the exposure and outcome			**2**	**1**	**2**		
c. Sample size needed to detect associations			**3**				**2**
d. Potential for follow-up/tracking			**1**		**2**	**1**	**1**
e. Generalizability to total population at risk			**1**		**2**		**2**
Overall rating for NCS Study Design Considerations			**3**	**1**	**1**		

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **0** No response
- **1** No basis to judge
- **3** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **1** Other (not enough support in the literature for this hypothesis)

Please rate the need for further research:

- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **4** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
3	**1**	**0**	**0**	**1**

HYPOTHESIS #7

Exposure to solvents and paints may increase the risk of childhood cancers, including leukemia and brain tumors.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- The sample size is too low, and the hypothesis is not original. (Reviewer #3)
- One hundred thousand children is not likely to yield enough cases of any particular kind of childhood cancer. Even in a cohort study, good measurement of solvent exposure is likely to be hard to achieve. (Reviewer #4)
- It would be useful but not feasible with the sample size of the study. (Reviewer #5)

LOW to MEDIUM

- Mechanistically, this is poorly explained. There are apparently few, if any, studies demonstrating correlational links. This hypothesis is too hypothetical. If studies showed a stronger link, then include the hypothesis, otherwise, omit it. The timing of the exposure is also important to consider. If it's prenatal, I am not sure how it would be measured. (Reviewer #1)

HIGH

- This hypothesis is of potentially high importance but is very difficult to carry out. It would require prospective studies in stable populations. (Reviewer #2)

HYPOTHESIS #8

Exposure to insecticides/pesticides may increase the risk of childhood cancers, including leukemia and lymphomas.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**3**		**1**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual							**5**
➢ for population/society			**2**	**1**	**1**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual							**5**
➢ for population/society			**3**		**1**		**1**
d. Frequency/load of exposure					**3**		**2**
e. Special populations in which exposure/disease outcome appears		**1**	**1**		**2**		**1**
Overall rating for Public Health Significance			**1**		**1**	**1**	**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**2**		**2**		**1**
b. Ascertaining the exposure and outcome			**1**		**4**		
c. Sample size needed to detect associations			**3**				**2**
d. Potential for follow-up/tracking					**3**	**1**	**1**
e. Generalizability to total population at risk			**1**		**2**		**2**
Overall rating for NCS Study Design Considerations			**3**		**1**	**1**	

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **1** No response
- **0** No basis to judge
- **2** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
4	**0**	**0**	**1**	**0**

HYPOTHESIS #8

Exposure to insecticides/pesticides may increase the risk of childhood cancers, including leukemia and lymphomas.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- There has been much written about this, but with no clear indication of a causal relationship. There are just too many variables and confounders. There are hundreds of insecticides and pesticides. It is wrong to assume the collective term covers comparable insecticides and pesticides. The hypothesis needs to be very precise. This hypothesis is low level of importance because preliminary data from experimental animal studies is still needed. (Reviewer #2)

- The sample size is too low, and the hypothesis is not original. (Reviewer #3)

- One hundred thousand children is not likely to yield enough cases of any particular kind of childhood cancer to justify this endpoint. Some pesticide residues can be measured in blood or breast milk, but others might be hard to measure. (Reviewer #4)

- The power of the study and the ability to ascertain the exposure are both problems. (Reviewer #5)

MEDIUM to HIGH

- This hypothesis is especially important if linked to genetic predisposition studies. It also relates to the larger issue of increased use of insecticides/pesticides. This hypothesis should be adopted. (Reviewer #1)

HYPOTHESIS #9

Exposure to paternal/maternal smoking may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**2**		**1**		**2**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual							**5**
➢ for population/society			**1**	**1**	**2**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual							**5**
➢ for population/society			**2**		**2**		**1**
d. Frequency/load of exposure					**2**		**3**
e. Special populations in which exposure/disease outcome appears		**2**	**1**		**1**		**1**
Overall rating for Public Health Significance						**1**	**4**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome					**3**		**2**
b. Ascertaining the exposure and outcome			**2**		**1**		**2**
c. Sample size needed to detect associations			**3**		**1**		**1**
d. Potential for follow-up/tracking			**1**		**1**	**1**	**2**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations			**1**	**1**	**2**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **3** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **4** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
2	**1**	**2**	**0**	**0**

HYPOTHESIS #9

Exposure to paternal/maternal smoking may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- NCS' small sample size, the difficulty in ascertaining exposure, and increasing cancer rates despite decreasing postnatal smoking make this a hypothesis of low importance. (Reviewer #3)

- One hundred thousand children is not likely to yield enough cases of any particular kind of childhood cancer to justify this outcome. Otherwise, it would be a good hypothesis, although not very novel. (Reviewer #4)

LOW to MEDIUM

- Again there are sample size issues, but there are fewer problems with ascertainment of exposure for this hypothesis. (Reviewer #5)

MEDIUM

- Smoking and ETS appear to be more important etiological agents in other high prevalence diseases, especially asthma. The actual clinical impact of this factor on the incidence of cancer may be very small. In addition, lung cancer is beyond the scope of the study. This hypothesis should be modified to focus on measurable childhood outcomes. Genetic predisposition probably plays a role. (Reviewer #1)

- This hypothesis combines too many variables and is not specific enough. Does the exposure occur once or is it a constant, frequent exposure to tobacco smoke? It is conceivable that the exposure is pre-natal vs. post-natal. Why limit it to maternal or paternal smoking? What about exposure to environmental tobacco smoke. This hypothesis is of medium importance but needs to be refined and more precise regarding the type and timing of the exposure. (Reviewer #2)

HYPOTHESIS #10

Exposure to infectious agents/viruses may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**1**	**2**		**1**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**1**					**4**
➢ for population/society		**1**	**1**	**1**	**1**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**1**					**4**
➢ for population/society		**1**	**2**		**1**		**1**
d. Frequency/load of exposure		**2**			**1**		**2**
e. Special populations in which exposure/disease outcome appears		**2**			**2**		**1**
Overall rating for Public Health Significance	**1**					**1**	**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**1**	**1**		**2**		**1**
b. Ascertaining the exposure and outcome		**1**	**2**		**1**		**1**
c. Sample size needed to detect associations		**1**	**3**				**1**
d. Potential for follow-up/tracking		**1**			**2**	**1**	**1**
e. Generalizability to total population at risk		**1**			**2**		**2**
Overall rating for NCS Study Design Considerations		**1**	**3**			**1**	

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **3** No basis to judge
- **1** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **1** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
4	**0**	**0**	**1**	**0**

HYPOTHESIS #10

Exposure to infectious agents/viruses may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis has too many variables to make sense. There are a variety of infectious agents. Viruses are a type of infectious agents. Viral etiology of cancer has been studied for eighty years without any useful information coming from the research. This hypothesis is not worth studying because ongoing research is already being performed for specific infections agents; it therefore is of low importance. (Reviewer #2)

- The sample size is much too small, and the exposures are difficult to measure. In addition, the hypothesis does not specify which infectious agents to study. (Reviewer #3)

- One hundred thousand children is not likely to yield enough cases of any particular kind of childhood cancer to justify this outcome. Otherwise, this would be a good hypothesis. Study of infectious agents was a very productive area in the Collaborative Perinatal Project, mainly using stored serum for immunologic studies. (Reviewer #4)

- This hypothesis has low feasibility. (Reviewer #5)

MEDIUM to HIGH

- This is especially important if linked to other farm/rural related issues such as the use of pesticides. This hypothesis should be adopted. (Reviewer #1)

HYPOTHESIS #11

Increased fetal exposure to endocrine disrupters may result in reproductive and physiological abnormalities.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**1**		**3**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**1**	**1**	**1**	**1**		**1**
➢ for population/society		**2**	**1**		**2**		
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**3**	**1**				**1**
➢ for population/society		**3**	**1**		**1**		
d. Frequency/load of exposure		**2**	**1**		**1**		**1**
e. Special populations in which exposure/disease outcome appears		**2**	**1**			**1**	**1**
Overall rating for Public Health Significance	**1**		**1**		**2**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**1**	**2**		**1**		**1**
b. Ascertaining the exposure and outcome			**3**		**1**		**1**
c. Sample size needed to detect associations		**1**	**1**		**1**		**2**
d. Potential for follow-up/tracking			**1**		**3**		**1**
e. Generalizability to total population at risk		**1**		**1**	**1**		**2**
Overall rating for NCS Study Design Considerations			**3**		**1**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **1** No response
- **1** No basis to judge
- **0** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **1** No basis to judge
- **1** Not needed at all
- **2** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
3	**0**	**1**	**0**	**1**

HYPOTHESIS #11

Increased fetal exposure to endocrine disrupters may result in reproductive and physiological abnormalities.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- Though potentially important, the exposures and outcomes are not well defined other than hypospadius. The timeframes for some outcomes (e.g., male fertility) may also be difficult to study. This hypothesis is way out of focus. Endocrine disrupters are an increasing area of concern. My sense is this is a broad approach that isn't too helpful. This hypothesis should be omitted. (Reviewer #1)

- There is a need to answer this question, but the answer should be sought in initial animal experimentation. The influences are too diffuse. (Reviewer #2)

- Again the outcomes are rare and the sample size questionable. Both the exposure and the outcomes are an issue. PCBs stay in the body and can quantify the exposure better. The outcomes are tougher in terms of measurability. There is also a question of when the effects would be detectable. (Reviewer #5)

MEDIUM

- Exposure ascertainment needs improvement, especially regarding which endocrine disrupters to measure and at what time. (Reviewer #3)

HIGH

- Role of environmental endocrine disrupters in human health is still largely a matter of speculation. A few animal models suggest that careful inquiry is necessary. Seems highly relevant to NCS. (Reviewer #4)

HYPOTHESIS #12

Exposure to contaminants in water, such as chlorine disinfection byproducts, can lead to adverse birth outcomes such as neural tube defects, low birth weight, and spontaneous abortions.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**2**					**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**2**			**1**		**2**
➢ for population/society		**2**					**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**2**			**1**		**2**
➢ for population/society		**2**					**3**
d. Frequency/load of exposure		**2**					**3**
e. Special populations in which exposure/disease outcome appears		**3**					**2**
Overall rating for Public Health Significance		**1**			**1**		**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**	**1**			**1**		**2**
b. Ascertaining the exposure and outcome		**1**	**1**		**1**		**2**
c. Sample size needed to detect associations		**1**					**4**
d. Potential for follow-up/tracking		**1**			**2**		**2**
e. Generalizability to total population at risk		**1**			**1**		**3**
Overall rating for NCS Study Design Considerations		**1**			**2**		**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **2** No basis to judge
- **2** This hypothesis addresses established research
- **1** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **1** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
2	**0**	**1**	**0**	**2**

HYPOTHESIS #12

Exposure to contaminants in water, such as chlorine disinfection byproducts, can lead to adverse birth outcomes such as neural tube defects, low birth weight, and spontaneous abortions.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- I do not know of any evidence that chlorinated water causes adverse birth outcomes. Chlorinated water has been used for a long time now; we would have seen its effects by now. This is not my field of work and I have no basis to judge other contaminants. If one found clusters where water had greater quantities of a contaminant than are generally found, it could warrant a study. Still, this has been addressed in the previous hypotheses and is too vague to support a study. (Reviewer #2)

- Misclassification of the exposure is a serious problem. It is tough to measure the exposure in a stable way. (Reviewer #5)

MEDIUM

- I am not clear what NCS can add that is original or improved relative to previous research. (Reviewer #3)

HIGH

- This has been a longstanding controversy, and has become more important now with the increased awareness of the importance of oral health. Although this has been looked at in the past, it would be good to lay this to rest. This hypothesis should be adopted. (Reviewer #1)

- NCS provides a unique opportunity to see whether exposures to chlorine disinfection byproducts in pregnancy or early childhood are associated with common birth defects (pregnancy) or other childhood health outcomes occurring in more than about 1.5/1000 children. (Reviewer #4)

HYPOTHESIS #13

Exposure to environmental toxicants, such as air pollutants and DEHP (di-2-ethylhexyl phthalate), can affect various stages of child development, from intrauterine to postnatal development.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition	**1**	**4**					
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual	**1**	**4**					
➢ for population/society	**1**	**3**					**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual	**1**	**4**					
➢ for population/society	**1**	**3**					**1**
d. Frequency/load of exposure	**1**	**2**			**1**		**1**
e. Special populations in which exposure/disease outcome appears	**1**	**2**					**2**
Overall rating for Public Health Significance	**2**	**2**					**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**2**			**1**		**2**
b. Ascertaining the exposure and outcome		**1**	**1**		**2**		**1**
c. Sample size needed to detect associations		**2**					**3**
d. Potential for follow-up/tracking		**1**	**1**		**2**		**1**
e. Generalizability to total population at risk		**1**			**1**		**3**
Overall rating for NCS Study Design Considerations		**1**	**1**		**2**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **0** No response
- **3** No basis to judge
- **2** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:

- **0** No response
- **1** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**2**	**0**	**1**

HYPOTHESIS #13

Exposure to environmental toxicants, such as air pollutants and DEHP (di-2-ethylhexyl phthalate), can affect various stages of child development, from intrauterine to postnatal development.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis is not focused or specific enough; too many factors are included. Different substances may have entirely different effects. What is being targeted at what point in time? There is no doubt that environmental substances affect intrauterine development. This hypothesis needs more focus; it is too vague to study. (Reviewer #2)

- Again the methodology seems problematic, in terms of quantifying the exposure and outcomes. There were not enough data presented to support the usefulness of pursuing this hypothesis; the review papers did not provide empirical data to support further research. (Reviewer #5)

MEDIUM

- This hypothesis needs to identify associated outcomes, especially for DEHP. (Reviewer #3)

- Will need to focus scope of the hypothesis because currently it involves two very different types of exposures, phthalates (which are plastics) and air pollution. NCS is not likely to be optimally designed to study air pollution effects due to reasons mentioned earlier (e.g., children in cluster sample will be exposed to similar levels of air pollution and results will only provide the differences among different centers). Study of phthalate exposures might be of interest – they are related to endocrine disrupter issues. Issue of whether they can be satisfactorily measured in large numbers of subjects needs inquiry. (Reviewer #4)

HIGH

- This hypothesis adds a developmental dimension (increases susceptibility) to the NCS and needs to be coupled with genetic predisposition studies, and not linked to any specific outcomes. This is a methodological hypothesis in that it is more focused on saying the timing of exposure has an effect. It is not looking at specific outcomes but instead looks at different stages which may have different effects. I would adopt the concept rather than the hypothesis. The question should be what are the developmental windows of vulnerability to impact various exposures and susceptibility to their influences. (Reviewer #1)

HYPOTHESIS #14

Exposure to environmental toxicants such as pesticides (e.g., organophosphates) can play a causal role in childhood diseases ranging from asthma to neurological disorders.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition	**2**	**1**			**1**		**1**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual	**2**	**2**					**1**
➢ for population/society	**2**	**2**					**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual	**2**	**2**					**1**
➢ for population/society	**2**	**2**					**1**
d. Frequency/load of exposure	**1**				**2**		**2**
e. Special populations in which exposure/disease outcome appears	**1**	**2**					**2**
Overall rating for Public Health Significance	**1**	**1**			**2**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**2**				**2**		**1**
b. Ascertaining the exposure and outcome	**2**				**2**		**1**
c. Sample size needed to detect associations	**1**	**1**					**3**
d. Potential for follow-up/tracking	**1**				**2**	**1**	**1**
e. Generalizability to total population at risk	**1**				**1**		**3**
Overall rating for NCS Study Design Considerations	**2**				**2**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **1** No response
- **1** No basis to judge
- **1** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **1** No response
- **0** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance: (1 review did not rate this hypothesis)

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
1	**0**	**2**	**1**	**0**

HYPOTHESIS #14

Exposure to environmental toxicants such as pesticides (e.g., organophosphates) can play a causal role in childhood diseases ranging from asthma to neurological disorders.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

NO RATING PROVIDED

- This hypothesis has already been presented in the targeted research area of asthma and respiratory illnesses. (Reviewer #2)

LOW

- The outcomes are poorly specified (except for asthma). (Reviewer #3)

MEDIUM

- Pesticides have been examined to a considerable extent, but there are now some new, modern pesticides. Estimating exposure to some of these agents could be problematic. Some pesticides such as organophosphate, are possible to measure in adipose tissue, but some of the modern pesticides are harder to measure because they are more ubiquitous in the child's environment; therefore measuring exposure would not be straightforward. Despite these problems, exposure to these toxic agents should be considered for inclusion in the NCS. (Reviewer #4)

- The link to risk is not clear, but if toxic, it may be very important. I am familiar with some direct, acute toxic effects of organophosphate exposure, which are more measurable. (Reviewer #5)

MEDIUM to HIGH

- This is especially important when linked to genetic predisposition studies, as in Hypothesis #8 relating to pesticides and cancer. It also relates to the larger issue of increased use of insecticides/pesticides. How to measure the exposure and the importance of the gene environment are important considerations. This hypothesis is broad. I would modify it to include not just neurological disorders, but also neurodevelopmental (e.g., cognitive, behavioral) outcomes. (Reviewer #1) (NOTE: Reviewer #1 did not provide a rate the "public health significance" for this hypothesis because there are multiple outcomes to rate.)

HYPOTHESIS #15

Factors in the immediate environment surrounding children (e.g., instability in the home, household composition) can be major risk factors in the incidence of childhood injury.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**1**					**4**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**1**			**1**		**3**
➢ for population/society		**1**					**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**1**			**1**		**3**
➢ for population/society		**1**					**4**
d. Frequency/load of exposure		**1**					**4**
e. Special populations in which exposure/disease outcome appears		**2**					**3**
Overall rating for Public Health Significance	**1**	**1**					**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**1**			**1**	**1**	**2**
b. Ascertaining the exposure and outcome		**1**			**1**		**3**
c. Sample size needed to detect associations		**1**					**4**
d. Potential for follow-up/tracking		**1**		**1**	**2**		**1**
e. Generalizability to total population at risk		**1**			**1**		**3**
Overall rating for NCS Study Design Considerations		**1**	**1**		**2**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **1** No basis to judge
- **4** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **1** No basis to judge
- **1** Not needed at all
- **1** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance: (1 reviewer indicated "no basis to judge")

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
1	**0**	**1**	**0**	**2**

HYPOTHESIS #15

Factors in the immediate environment surrounding children (e.g., instability in the home, household composition) can be major risk factors in the incidence of childhood injury.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

NO BASIS TO JUDGE to LOW

- This is not my area of expertise, but I do not think child abuse should be studied in the rubric of injuries. The problem is very complicated and it deserves a separate category. There is no a priori reason to hypothesize that chaos in the household implies neglect. (Reviewer #2)

LOW

- I do not believe the very expensive cohort approach will provide much more insight into the relation of these factors to childhood injury than would well conducted case-control studies. There is much less need to measure the exposures ahead of time than there is for some of the biological hypotheses. Moreover, even if refinements in our understanding resulted from the cohort approach, the issues under examination are not easy to intervene on so that the public health payoff might be limited. (Reviewer #4)

MEDIUM

- I am not clear on what NCS can do that is new or improved over previous studies. (Reviewer #3)

HIGH

- The incidence and prevalence of injury and mental (family) health issues are increasing. If home environment is broadly defined, the multiplicity of factors (exposures) would warrant a large study population. This hypothesis should be adopted. (Reviewer #1)

- This is an important issue calling for a longitudinal study on a large scale to control for confounding issues such as the economic changes associated with changes in household composition, social disruption (getting better or worse), and changes in the physical environment. (Reviewer #5)

HYPOTHESIS #16

Children who are exposed to physical and psychological stress due to large disruptions in their broader community/social environment, such as war, natural disasters (e.g., hurricanes, bombings, large-scale accidents such as crashes), and poverty may be at high risk for developing complex psychological problems (in addition to physical injuries) due to deaths in the family, home damage, and displacement.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**1**			**1**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**1**			**2**		**2**
➢ for population/society		**1**			**1**		**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**1**			**1**		**3**
➢ for population/society		**1**			**1**		**3**
d. Frequency/load of exposure		**1**	**1**				**3**
e. Special populations in which exposure/disease outcome appears		**2**					**3**
Overall rating for Public Health Significance		**1**			**1**		**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**	**1**			**1**		**2**
b. Ascertaining the exposure and outcome	**1**	**1**			**1**		**2**
c. Sample size needed to detect associations		**2**			**1**		**2**
d. Potential for follow-up/tracking		**1**	**1**		**1**	**1**	**1**
e. Generalizability to total population at risk		**1**			**1**		**3**
Overall rating for NCS Study Design Considerations		**1**	**1**	**1**	**1**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **2** No basis to judge
- **2** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **1** No basis to judge
- **1** Not needed at all
- **2** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance: (1 reviewer indicate "no basis to judge")

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
3	**0**	**0**	**0**	**1**

HYPOTHESIS #16

Children who are exposed to physical and psychological stress due to large disruptions in their broader community/social environment, such as war, natural disasters (e.g., hurricanes, bombings, large-scale accidents such as crashes), and poverty may be at high risk for developing complex psychological problems (in addition to physical injuries) due to deaths in the family, home damage, and displacement.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

NO BASIS TO JUDGET to LOW

- This is not my area of expertise, but I know that there have been major, rather carefully conducted studies with clear outcomes. Physical injuries are not as important as emotional stress. Many studies were done in the U.K. during WWII. (Reviewer #2)

LOW

- Given the magnitude of the external exposures described and the frequency of the outcomes, existing data set analysis should help focus this hypothesis. As stated, a cohort study would be difficult to design to answer this. I think this could be studied with other approaches. Measuring specific stresses is hard to do. This hypothesis should be omitted. (Reviewer #1)

- This hypothesis seems trivial and has uncertain public health implications. (Reviewer #3)

- There can be no assurance that there will be natural disasters that will affect some CDS children more than others. Even if relationships were found, interventions are likely to be difficult and public health payoff low. (Reviewer #4)

HIGH

- It would be important to study this hypothesis. If there's a disaster, the dislocations that occur are enormous. Exposure is not a problem, but the kids would be tough to track, especially when they are moved from where they are. I would suggest that the study not look just at the negative side of the outcomes. One should also look at individuals who bounce back and/or continue to thrive and don't manifest problems. The study needs to include measures to assess resiliency as well as risk. An extra effort would be needed to track subjects because of likely disruptions in their lives and living arrangements. (Reviewer #5)

HYPOTHESIS #17

As children grow and spend more time in the exterior environment, they are exposed to factors in the modern built environment that place them at risk for injury and death. The quality and structural safety of buildings, traffic, and play areas may affect the chance of incurring illness, disability, or injury. Poor construction and structural hazards may be leading causes for the prevalence of childhood falls, burnings, drownings, and secondary harms and diseases.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual				**1**			**4**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**1**		**4**
➢ for population/society							**5**
d. Frequency/load of exposure					**2**		**3**
e. Special populations in which exposure/disease outcome appears		1			**1**		**3**
Overall rating for Public Health Significance							**5**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**				**1**	**1**	**2**
b. Ascertaining the exposure and outcome					**3**		**2**
c. Sample size needed to detect associations			**1**		**3**		**1**
d. Potential for follow-up/tracking				**1**	**1**		**3**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations			**2**		**2**	**1**	

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **4** This hypothesis addresses established research
- **1** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **2** Not needed at all
- **1** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
3	**0**	**1**	**1**	**0**

HYPOTHESIS #17

As children grow and spend more time in the exterior environment, they are exposed to factors in the modern built environment that place them at risk for injury and death. The quality and structural safety of buildings, traffic, and play areas may affect the chance of incurring illness, disability, or injury. Poor construction and structural hazards may be leading causes for the prevalence of childhood falls, burnings, drownings, and secondary harms and diseases.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- There is no need for additional data. The problem is well understood and potential solutions are known. These solutions need to be implemented. (Reviewer #2)

- This hypothesis seems trivial. I am not clear that further research is needed, unless specific hazards are more detailed. (Reviewer #3)

- Seems unlikely that cohort approach can add much to what we have learned from the many other studies of causes of injury in children. (Reviewer #4)

MEDIUM

- Although this is very important to study, I question the feasibility of accurately measuring exposures. Kids are all over the place. Which structural hazards should be studied? Where? Hazards exist not just in the home but also at friends' houses, playgrounds, summer vacations, etc. This hypothesis would require a multitude of measurements. (Reviewer #5)

MEDIUM to HIGH

- This hypothesis looks at multiple measures and outcomes and requires a large cohort. This hypothesis should be adopted. (Reviewer #1)

HYPOTHESIS #18

Children may be at high risk for injury due to psychosocial factors in environments outside the home. Children who experience psychosocial stress in schools may be prone to aggressive or violent behavior, resulting in unintentional and/or intentional injury to oneself and others. School environments that exhibit high rates of psychosocial problems may also exhibit high rates of sports-related injuries among children and physical violence between children.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**1**		**1**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**3**		**2**
➢ for population/society			**1**		**2**		**2**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**		**3**
➢ for population/society					**3**		**2**
d. Frequency/load of exposure		**1**			**1**		**3**
e. Special populations in which exposure/disease outcome appears		**2**					**3**
Overall rating for Public Health Significance	**1**				**2**	**1**	**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**1**		**3**		**1**
b. Ascertaining the exposure and outcome					**3**		**2**
c. Sample size needed to detect associations		**1**			**2**		**2**
d. Potential for follow-up/tracking					**2**		**3**
e. Generalizability to total population at risk					**3**		**2**
Overall rating for NCS Study Design Considerations			**1**		**4**		

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **1** This hypothesis addresses established research
- **4** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **4** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
2	**0**	**3**	**0**	**0**

HYPOTHESIS #18

Children may be at high risk for injury due to psychosocial factors in environments outside the home. Children who experience psychosocial stress in schools may be prone to aggressive or violent behavior, resulting in unintentional and/or intentional injury to oneself and others. School environments that exhibit high rates of psychosocial problems may also exhibit high rates of sports-related injuries among children and physical violence between children.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis is of low importance for immediate study. The proposed study design would allow for adding this aspect as the cohort reaches school age. There may be better research later to inform how to study this instead of just studying it now. Buying time to develop the hypothesis may be better; we may be better informed five years into the study. (Reviewer #1)

- The hypothesis does not use all the prenatal and perinatal information that will be collected in NCS. It would require detailed measurement of school characteristics. Most of these problems occur at later ages. (Reviewer #4)

MEDIUM

- This is a worthwhile effort, but both the potential study and any remedies are culture-bound. There are different degrees of discipline and restricted behavior in different cultures. Some societies, for example, are more permissive while others are more restrictive. Timing, such as the length of time in school, needs to be considered. It would be necessary to know exactly the medium in which the children are being assessed. (Reviewer #2)

- Psychosocial sequelae are probably more important outcomes than injuries. (Reviewer #3)

- The school area is an unstudied element. I am less interested in the sports-related injury aspect of the hypothesis. Victimization (e.g., teasing, picking on) may be an issue to examine. I would modify this hypothesis, dropping the last part and instead look at the effect on self-esteem, ability to learn, and attitudes towards differences in kids. (Reviewer #5)

HYPOTHESIS #19

Organophosphate pesticides such as PCBs, PCDDs, and PCDFs have a detrimental impact on neurodevelopment, causing functional, neurologic, and cognitive expression.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**2**					**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**2**	**1**		**2**		
➢ for population/society		**2**			**2**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**2**	**2**		**1**		
➢ for population/society		**1**			**2**		**2**
d. Frequency/load of exposure		**1**			**1**		**3**
e. Special populations in which exposure/disease outcome appears	**1**	**2**					**2**
Overall rating for Public Health Significance		**1**			**2**		**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**2**				**3**
b. Ascertaining the exposure and outcome			**1**		**2**	**1**	**1**
c. Sample size needed to detect associations	**1**		**1**		**1**		**2**
d. Potential for follow-up/tracking			**1**		**3**		**1**
e. Generalizability to total population at risk			**1**		**1**		**3**
Overall rating for NCS Study Design Considerations			**1**		**2**		**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **0** No response
- **1** No basis to judge
- **2** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:

- **0** No response
- **1** No basis to judge
- **0** Not needed at all
- **2** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
1	**0**	**2**	**0**	**2**

HYPOTHESIS #19

Organophosphate pesticides such as PCBs, PCDDs, and PCDFs have a detrimental impact on neurodevelopment, causing functional, neurologic, and cognitive expression.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- All of these studies listed under this hypothesis are the ones relating to asthma and cancer and suffer from confounders that make a clear cut result impossible. All correlations are reported as "weak" and all reports request future studies. Lead is an exception. There are good data relating to its influence on brain development. (Reviewer #2)

MEDIUM

- I am not clear how (besides larger sample size) NCS will improve on previous studies. (Reviewer #3)

- There has been some work in this area, but a large cohort study could add information. Careful study of special populations with higher exposures might be more informative, however. The most likely finding would be modest associations for which causality will be hard to judge. (Reviewer #4)

HIGH

- The increasing incidence of outcomes and the prevalence of the exposure warrant further study. A major issue in this hypothesis would be measuring in utero exposure. This hypothesis should be adopted. (Reviewer #1)

- I would rate this high although there is some uncertainty about the actual impact. It would be important to know the answer either way. (Reviewer #5)

HYPOTHESIS #20

Autism is a neurodevelopmental disease that may be linked to components of vaccines and immunizations and may have a genetic link.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**2**		**2**	**1**	
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual							**5**
➢ for population/society			**1**		**3**		**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual							**5**
➢ for population/society			**1**		**3**		**1**
d. Frequency/load of exposure		**3**					**2**
e. Special populations in which exposure/disease outcome appears	**1**	**3**	**1**				
Overall rating for Public Health Significance	**2**			**1**	**1**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**1**	**1**				**3**
b. Ascertaining the exposure and outcome		**1**	**2**		**1**		**1**
c. Sample size needed to detect associations			**1**		**1**		**3**
d. Potential for follow-up/tracking					**2**	**1**	**2**
e. Generalizability to total population at risk		**1**	**1**		**2**		**1**
Overall rating for NCS Study Design Considerations			**2**		**1**		**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **1** No basis to judge
- **2** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **1** Not needed at all
- **3** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**1**	**1**	**1**

HYPOTHESIS #20

Autism is a neurodevelopmental disease that may be linked to components of vaccines and immunizations and may have a genetic link.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- There have been sufficient studies concerning environmental influences on the etiology of autism. These have not revealed any positive correlations. The apparent increase in the incidence of autism can be explained by better diagnostic criteria. There's absolutely no evidence that MMR or other vaccines are causally related. (Reviewer #2)

- There are too many theories, and this is an inadequate sample size given the incidence of autism. At most, 200 kids in the study may have it. Trying to loot at genetic subgroups in this sample would be difficult. Also, there is already enough research about autism and vaccines. (Reviewer #5)

MEDIUM

- No environmental exposures and ideas about how to study vaccine effects in face of near-universal vaccination have been specified in detail. (Reviewer #3)

MEDIUM to HIGH

- This is a politically highly visible issue. The genetic aspect is very appealing and may serve as a model for other hypotheses and future studies. This hypothesis is methodologically appealing and should be adopted. (Reviewer #1)

HIGH

- Autism is thought by many to be increasing in prevalence. Prospective studies to look for causes are needed and the NCS will be about the right size. The trick will be to identify the right exposures to measure besides family history. Getting a good vaccine history is probably a good idea. (Reviewer #4)

HYPOTHESIS #21

Stress, neglect, and trauma caused by child abuse and maltreatment have adverse affects on a child's neurodevelopment.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**1**		**1**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**1**	**1**	**3**
➢ for population/society					**2**		**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**2**	**1**	**2**
➢ for population/society					**2**		**3**
d. Frequency/load of exposure		**1**	**1**				**3**
e. Special populations in which exposure/disease outcome appears		**1**	**2**				**2**
Overall rating for Public Health Significance						**2**	**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**2**		**2**		**1**
b. Ascertaining the exposure and outcome			**3**		**2**		
c. Sample size needed to detect associations					**2**	**1**	**2**
d. Potential for follow-up/tracking			**1**	**1**	**3**		
e. Generalizability to total population at risk					**4**		**1**
Overall rating for NCS Study Design Considerations			**1**		**3**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **0** No response
- **0** No basis to judge
- **5** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:

- **0** No response
- **0** No basis to judge
- **1** Not needed at all
- **2** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
1	**0**	**3**	**0**	**1**

HYPOTHESIS #21

Stress, neglect, and trauma caused by child abuse and maltreatment have adverse affects on a child's neurodevelopment.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- Abuse will be hard to document. Moreover, abuse discovered in the NCS will need to be referred for intervention – which will make it hard to study. We already know that abuse is bad, so it is difficult to see the benefit of pursuing this hypothesis. (Reviewer #4)

MEDIUM

- This is a serious social problem, but research possibilities are limited. (Reviewer #2)

- This hypothesis is vague as stated – almost trivial. Specific exposures and outcomes are difficult (but not impossible) to measure. I am not clear what NCS can do better than previous studies. (Reviewer #3)

- There is an issue regarding the ability to measure the exposure to stress and neglect. Measuring stress and neglect is very subjective and difficult to quantify. Despite the difficulty of assessing these exposures, however, this hypothesis would require a large sample studied longitudinally. (Reviewer #5)

HIGH

- This is related to Hypothesis #16 but is better focused and articulated. It deals more with a continued stressful environment rather than an event. This hypothesis should be adopted. (Reviewer #1)

HYPOTHESIS #22

Maternal immune response to infections can have an adverse effect on the fetus' neurodevelopment.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**3**					**2**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**4**			**1**		
➢ for population/society		**4**					**1**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**4**			**1**		
➢ for population/society		**4**					**1**
d. Frequency/load of exposure		**3**					**2**
e. Special populations in which exposure/disease outcome appears	**1**	**2**	**1**				**1**
Overall rating for Public Health Significance	**2**	**1**					**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**	**1**			**1**		**2**
b. Ascertaining the exposure and outcome		**3**			**1**		**1**
c. Sample size needed to detect associations		**2**	**1**				**2**
d. Potential for follow-up/tracking		**1**			**3**		**1**
e. Generalizability to total population at risk	**1**	**2**			**1**		**1**
Overall rating for NCS Study Design Considerations		**1**	**1**		**2**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **3** No basis to judge
- **0** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **3** No basis to judge
- **1** Not needed at all
- **1** Somewhat needed
- **0** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
3	**0**	**1**	**0**	**1**

HYPOTHESIS #22

Maternal immune response to infections can have an adverse effect on the fetus' neurodevelopment.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This hypothesis is interesting but is very vague with few specifics (e.g., all infections or specific infections with predilection to developing neural tissue). This hypothesis needs further development and preliminary research support (e.g., from other mammalian models). It is very speculative unless there are better data regarding potential mechanisms. I am not sure this is one I would include. (Reviewer #1)

- This is a very confusing hypothesis with no apparent cohesion. The hypothesis is naïve and not worth studying. The study design is not sufficient to study this hypothesis. (Reviewer #2)

- There is insufficient evidence for the effect of this type of infection and a low likelihood of detecting adult mental health problems unless the subjects are more than 20 years of age. (Reviewer #5)

MEDIUM

- Obtaining and storing maternal serum will be prudent; neurodevelopmental outcomes are an important endpoint. Therefore, the possibility of studying this hypothesis is strong, even though the hypothesis itself seems a bit of a long shot. (Reviewer #4)

HIGH

- There is little information available in the literature, but this hypothesis requires extensive data on maternal response (biomarkers) throughout pregnancy. (Reviewer #3)

HYPOTHESIS #23

In utero and postnatal exposure to methylmercury has adverse effects on a child's neurodevelopment and biobehavioral development.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**1**			**1**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual			**3**		**2**		
➢ for population/society		**1**	**1**		**1**		**2**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**1**	**2**		**2**		
➢ for population/society		**2**			**1**		**2**
d. Frequency/load of exposure		**1**	**1**		**1**	**1**	**1**
e. Special populations in which exposure/disease outcome appears	**1**	**1**			**1**		**2**
Overall rating for Public Health Significance		**1**			**3**		**1**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**		**1**				**3**
b. Ascertaining the exposure and outcome			**1**				**4**
c. Sample size needed to detect associations					**1**		**4**
d. Potential for follow-up/tracking	**1**				**3**		**1**
e. Generalizability to total population at risk	**1**				**1**		**3**
Overall rating for NCS Study Design Considerations					**2**	**1**	**2**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **3** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **3** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
0	**0**	**2**	**0**	**3**

HYPOTHESIS #23

In utero and postnatal exposure to methylmercury has adverse effects on a child's neurodevelopment and biobehavioral development.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

MEDIUM

- Because this is a simple pollutant, it is possible to carry out research with significant findings. (Reviewer #2)

- I am not clear what NCS can add to previous studies. One could expand this hypothesis to include ethylmercury. (Reviewer #3)

HIGH

- This is an essential hypothesis that this study should test. Timing and dose of in utero exposure remain challenges. This hypothesis should be adopted. (Reviewer #1)

- This is a controversial area. The hypothesis does not require the full sample size of the NCS, but a sub-study involving part of the population would be of considerable interest. (Reviewer #4)

- It is important to determine if mercury has negative effects and would be difficult to study without a large scale longitudinal study. (Reviewer #5)

HYPOTHESIS #24

In utero and postnatal exposure to lead has adverse effects on a child's neurodevelopment and biobehavioral development.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**1**				**4**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**4**		**1**
➢ for population/society			**2**				**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**5**		
➢ for population/society			**2**				**3**
d. Frequency/load of exposure		**1**	**1**		**1**	**1**	**1**
e. Special populations in which exposure/disease outcome appears	**2**	**1**					**2**
Overall rating for Public Health Significance	**1**		**1**		**1**		**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**		**1**				**3**
b. Ascertaining the exposure and outcome							**5**
c. Sample size needed to detect associations							**5**
d. Potential for follow-up/tracking					**3**		**2**
e. Generalizability to total population at risk					**1**		**4**
Overall rating for NCS Study Design Considerations	**1**					**1**	**3**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **5** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **2** Not needed at all
- **2** Somewhat needed
- **1** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
1	**1**	**1**	**0**	**2**

HYPOTHESIS #24

In utero and postnatal exposure to lead has adverse effects on a child's neurodevelopment and biobehavioral development.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- Much is known about the effect of lead. What is needed is prevention. (Reviewer #2)

LOW to MEDIUM

- This has been studied to death and the bulk of evidence is already clear. There is no need for a study of this size and scope. (Reviewer #5)

MEDIUM

- Low-level lead exposure is common, but it is difficult to exclude the role of confounders, especially when studying the reasons or mechanisms of lead exposure. (Reviewer #3)

HIGH

- This hypothesis can be coupled with Hypothesis #23. This is an essential hypothesis that this study should test. Timing and dose of in utero exposure remains a challenge. (Reviewer #1)

- There is considerable controversy about how low a lead level is of concern. The NCS will provide an excellent opportunity to investigate neurodevelopmental associations at quite low lead levels. Moreover, should there be a threshold effect below which lead levels do not affect neurodevelopment, the NCS will be large enough to define it. It might be desirable to measure some other metals since in at least one study the concentrations of an array of amniotic fluid metals were substantially correlated. (The presence of high lead levels should be considered a marker for the presence of other metals.) (Reviewer #4)

HYPOTHESIS #25

Exposure to lead impairs fetal biobehavioral development by lowering IQ and increasing cognitive developmental dysfunction.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition	**1**		**1**				**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual	**1**		**1**		**2**		**1**
➢ for population/society	**1**		**2**				**2**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual	**1**		**1**		**3**		
➢ for population/society	**1**		**2**				**2**
d. Frequency/load of exposure	**1**	**1**	**1**		**1**		**1**
e. Special populations in which exposure/disease outcome appears	**2**	**1**					**2**
Overall rating for Public Health Significance	**1**		**1**		**1**		**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**		**1**		**1**		**2**
b. Ascertaining the exposure and outcome	**1**						**4**
c. Sample size needed to detect associations	**1**						**4**
d. Potential for follow-up/tracking	**1**				**2**		**2**
e. Generalizability to total population at risk	**1**				**1**		**3**
Overall rating for NCS Study Design Considerations	**1**				**1**		**3**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **4** This hypothesis addresses established research
- **0** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **1** No response
- **0** No basis to judge
- **2** Not needed at all
- **2** Somewhat needed
- **0** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance: (1 reviewer did not provide a rating)

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
2	**0**	**1**	**0**	**1**

HYPOTHESIS #25

Exposure to lead impairs fetal biobehavioral development by lowering IQ and increasing cognitive developmental dysfunction.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

NO RATING PROVIDED

- It is unclear how this is different from Hypotheses #23 and #24. The timing of the exposures in the literature cited is essentially the same. If Hypothesis #24 is studied well, the research will also address issues raised in this hypothesis. (Reviewer #1)

LOW

- As with Hypothesis #24, Much is known about the effect of lead. I do not believe that Nevin's data – which are only retrospective correlations – can be accepted on their face value. (Reviewer #2)

- Same as Hypothesis #24 except for the decreased ability to assess the critical period of exposure in pregnancy, if the study is already staring with pregnant women. (Reviewer #5)

MEDIUM

- For same reasons described in Hypothesis #24, I'd rate this hypothesis at a medium level of importance. Low-level lead exposure is common, but it is difficult to exclude the role of confounders, especially when studying the reasons or mechanisms of lead exposure. This hypothesis should be combined with Hypothesis #24. (Reviewer #3)

HIGH

- (Same as #24) There is considerable controversy about how low a lead level is of concern. The NCS will provide an excellent opportunity to investigate neurodevelopmental associations at quite low lead levels. Moreover, should there be a threshold effect below which lead levels do not affect neurodevelopment, the NCS will be large enough to define it. It might be desirable to measure some other metals since in at least one study the concentrations of an array of amniotic fluid metals were substantially correlated. (The presence of high lead levels should be a considered a marker for the presence of other metals.) (Reviewer #4)

HYPOTHESIS #26

Maternally related factors such as smoking, exposure to environmental tobacco smoke, and substance abuse during pregnancy negatively affect biobehavioral development.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition					**2**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**5**		
➢ for population/society					**2**		**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**1**			**3**		**1**
➢ for population/society		**1**			**1**		**3**
d. Frequency/load of exposure					**2**		**3**
e. Special populations in which exposure/disease outcome appears	**1**	**1**	**1**				**2**
Overall rating for Public Health Significance			**1**		**2**		**2**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome			**2**		**1**		**2**
b. Ascertaining the exposure and outcome					**1**		**4**
c. Sample size needed to detect associations					**1**	**1**	**3**
d. Potential for follow-up/tracking				**1**	**3**		**1**
e. Generalizability to total population at risk					**3**		**2**
Overall rating for NCS Study Design Considerations			**1**		**3**		**1**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **4** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **2** Not needed at all
- **1** Somewhat needed
- **2** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
1	**1**	**0**	**1**	**2**

HYPOTHESIS #26

Maternally related factors such as smoking, exposure to environmental tobacco smoke, and substance abuse during pregnancy negatively affect biobehavioral development.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- This is a difficult hypothesis because of confounding by differences between smokers and non-smokers, and also because of intervening variables such as infant illnesses. (Reviewer #4)

LOW to MEDIUM

- Much of these data are already available. (Reviewer #5)

MEDIUM to HIGH

- Smoking can be studied, but drug abuse would be more difficult to study. These two should not be linked. One cannot lump substances, since substances act differently. Even if psychosocial influences are similar, outcomes may be completely different. There have been many studies looking at cocaine exposure which have not been terribly productive. Studies of smoking and tobacco use and their effect on placental blood supply, for example, may be more productive. It is worth looking at individual substances, but this would have to be done well. This hypothesis would be of medium-to-high importance if smoking and substance abuse were not linked. (Reviewer #2)

HIGH

- There is increasing evidence of the impact of maternal factors, including mental health, on child health. I would particularly look at the effect of maternal mental health. This hypothesis should be adopted. (Note: I am a little biased because of my own research.) (Reviewer #1)

- This hypothesis is of high importance especially regarding maternal smoking during pregnancy and exposure to environmental tobacco smoke postnatally, but requires biomarkers for exposure and more sensitive brain imaging and psychological testing than in previous studies. (Reviewer #3)

HYPOTHESIS #27

Broader societal factors such as neighborhood and community conditions can adversely impact a child's biobehavioral development.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition		**1**			**1**		**3**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual		**1**			**2**		**2**
➢ for population/society		**1**			**1**		**3**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual		**2**			**1**		**2**
➢ for population/society		**2**					**3**
d. Frequency/load of exposure		**1**			**1**		**3**
e. Special populations in which exposure/disease outcome appears		**1**			**1**		**3**
Overall rating for Public Health Significance		**1**			**1**		**3**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome		**1**	**1**		**1**		**2**
b. Ascertaining the exposure and outcome		**1**	**1**		**3**		
c. Sample size needed to detect associations		**1**					**4**
d. Potential for follow-up/tracking		**1**	**1**	**1**	**1**		**1**
e. Generalizability to total population at risk		**1**			**3**		**1**
Overall rating for NCS Study Design Considerations		**1**	**1**		**3**		

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **1** No response
- **1** No basis to judge
- **0** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:

- **1** No response
- **1** No basis to judge
- **0** Not needed at all
- **0** Somewhat needed
- **3** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance: (1 reviewer indicated "no basis to judge")

LOW	**LOW/MEDIUM**	**MEDIUM**	**MEDIUM/HIGH**	**HIGH**
1	**0**	**0**	**2**	**1**

HYPOTHESIS #27

Broader societal factors such as neighborhood and community conditions can adversely impact a child's biobehavioral development.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

NO BASIS TO JUDGE

- No basis to judge. (Reviewer #2)

LOW

- Since families aggregate in neighborhoods by socio-economic status and ethnicity, it is likely to be very difficult to disentangle neighborhood effects from family characteristics. Also, serious characterization of neighborhoods would be difficult for a study like NCS. (Reviewer #4)

MEDIUM to HIGH

- The ascertainment of exposure and controlling for confounders are major concerns for this hypothesis. I like this hypothesis, but it is very broad. There seems to be a lot of literature coming out regarding this (e.g., from Tony Earls and Tom Boyce). I would adopt this hypothesis. (Reviewer #1)

- A large study is needed to tease out confounders in order to test this hypothesis. Putting all of this in a question one can study may be overly ambitious. (Reviewer #5)

HIGH

- This hypothesis will require extensive measurement of exposures at multiple postnatal time periods and of numerous confounders. (Reviewer #3)

HYPOTHESIS #28

Altered intrauterine environment can affect fetal development leading to childhood obesity. Contributing factors include exposure to maternal diabetes, maternal malnutrition, and increased birth weight, which can alter fetal glucose tolerance and gene expression.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition							**5**
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual					**1**		**4**
➢ for population/society					**1**		**4**
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual					**1**		**4**
➢ for population/society					**1**		**4**
d. Frequency/load of exposure					**1**		**4**
e. Special populations in which exposure/disease outcome appears	**1**				**2**		**2**
Overall rating for Public Health Significance							**5**

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome					**1**		**4**
b. Ascertaining the exposure and outcome							**5**
c. Sample size needed to detect associations							**5**
d. Potential for follow-up/tracking					**2**		**3**
e. Generalizability to total population at risk					**2**		**3**
Overall rating for NCS Study Design Considerations					**2**		**3**

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:
- **0** No response
- **0** No basis to judge
- **3** This hypothesis addresses established research
- **2** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:
- **0** No response
- **0** No basis to judge
- **0** Not needed at all
- **2** Somewhat needed
- **3** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
1	**0**	**1**	**0**	**3**

HYPOTHESIS #28

Altered intrauterine environment can affect fetal development leading to childhood obesity. Contributing factors include exposure to maternal diabetes, maternal malnutrition, and increased birth weight, which can alter fetal glucose tolerance and gene expression.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- The intrauterine environment has not changed so much over time to explain the current epidemic of obesity. Focusing on prenatal factors is missing the boat. We need hypotheses related to the postnatal environment. (Reviewer #3)

MEDIUM

- Most of the cited measures of "intra-uterine environment" can be obtained retrospectively, making it unnecessary to use the NCS to test this hypothesis. On the other hand, it is likely that NCS data will cover these areas so that it will be possible to use NCS to examine these issues. (Reviewer #4)

HIGH

- For this hypothesis, I would suggest postnatal factors (e.g., toxins) as well. Obesity is a major epidemic, and NCS really needs to address this issue. I would adopt this hypothesis. (Note: Dr. Whitaker is in my division). (Reviewer #1)

- It is not at all clear that the main problem derives from intrauterine exposure. Postnatal influences are extremely important. The studies proposed need to be done. (Reviewer #2)

- (Very high) This is probably the most important and feasible hypothesis in the bunch! This hypothesis requires a large scale longitudinal study, and has implications for both mental health and physical health. (Reviewer #5)

HYPOTHESIS #29

Infectious bacterial agents such as Helicobacter pylori, Staphylococcus aureus, and Escherichia coli and their toxins may be causal factors for SIDS.

I. Public Health Significance Please indicate the ***importance*** of each of the following aspects of the hypothesis to children's health or public health in general. Please check the appropriate box to indicate your response.	**No Rating Given**	**No Basis to Judge**	**LEVEL OF IMPORTANCE**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Prevalence or incidence of the disease or condition			**3**		**2**		
b. Clinical burden (e.g., mortality, morbidity, functional status) ➢ for individual			**1**				**4**
➢ for population/society			**2**		**3**		
c. Economic burden (e.g., health care costs, productivity loss) ➢ for individual			**2**				**3**
➢ for population/society			**2**		**3**		
d. Frequency/load of exposure		**2**	**1**				**2**
e. Special populations in which exposure/disease outcome appears	**1**	**1**	**1**		**1**		**1**
Overall rating for Public Health Significance	**1**		**2**		**2**		

II. NCS Study Design Considerations Please rate the ***feasibility and appropriateness*** of investigating each hypothesis in the context of the general design of the NCS.	**No Rating Given**	**No Basis to Judge**	**FEASIBILITY & APPROPRIATENESS**				
			Low	**Low/ Medium**	**Medium**	**Medium/ High**	**High**
a. Timing of exposure and outcome	**1**		**1**		**1**		**2**
b. Ascertaining the exposure and outcome	**1**		**1**		**2**		**1**
c. Sample size needed to detect associations	**1**		**1**		**1**		**2**
d. Potential for follow-up/tracking	**1**				**3**		**1**
e. Generalizability to total population at risk					**3**		**2**
Overall rating for NCS Study Design Considerations			**1**	**1**	**3**		

III. State of Research on the Topic (Experts marked all that applied)

Please rate the status of present research:

- **1** No response
- **1** No basis to judge
- **0** This hypothesis addresses established research
- **3** This hypothesis addresses new and emerging research
- **0** Other

Please rate the need for further research:

- **0** No response
- **0** No basis to judge
- **1** Not needed at all
- **4** Somewhat needed
- **0** Extremely necessary

IV. Overall rating of hypothesis in terms of level of importance:

LOW	LOW/MEDIUM	MEDIUM	MEDIUM/HIGH	HIGH
3	**1**	**1**	**0**	**0**

HYPOTHESIS #29

Infectious bacterial agents such as Helicobacter pylori, Staphylococcus aureus, and Escherichia coli and their toxins may be causal factors for SIDS.

V. Comments Provided by Expert Reviewers

The expert reviewers' comments are organized according to their rating of the overall level of importance of the hypothesis.

LOW

- There is no evidence that this hypothesis is worth pursuing. (Reviewer #2)
- SIDS incidence is declining. The evidence supporting the hypothesis is meager. (Reviewer #3)
- The sample is inadequate and the study would require frequent monitoring of infants who died from SIDS. The frequency of SIDS is low and decreasing. Another problem is the ascertainment of the exposure. How often will kids be seen in the study between the ages of 0 and 4 months, for example? (Reviewer #5)

LOW to MEDIUM

- This hypothesis is speculative and not well supported. I would omit this hypothesis. This hypothesis needs a strong genetic component. Why are some kids predisposed? (Reviewer #1)

MEDIUM

- The NCS is about the right size for a prospective study of SIDS. To the extent that bacteriologic risk factors can be measured immunologically with frozen serum this seems a reasonable hypothesis to go after. However, it would not seem worthwhile to culture the infants based on current evidence. (Reviewer #4)